The Management of Major Depressive Disorder: Synopsis of the 2022 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline

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Description: In February 2022, the U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) approved a joint clinical practice guideline (CPG) for the management of major depressive disorder (MDD). This synopsis summarizes key recommendations.

Methods: Senior leaders within the VA and the DoD assembled a team to update the 2016 CPG for the management of MDD that included clinical stakeholders and conformed to the National Academy of Medicine's tenets for trustworthy CPGs. The guideline panel developed key questions, systematically searched and evaluated the literature, created two 1-page algorithms, and distilled 36 recommendations for care using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Select recommendations that were identified by the authors to represent key changes from the prior CPG are presented in this synopsis.

Recommendations: The scope of the CPG is diverse; however, this synopsis focuses on key recommendations that the authors identified as important new evidence and changes to prior recommendations on pharmacologic management, pharmacogenomics, psychotherapy, complementary and alternative therapies, and the use of telemedicine.

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By many measures, depression is a devastating illness. In 2017, depressive disorders (including major depressive disorder [MDD] and persistent depressive disorder [PDD]) were ranked third in terms of years lived with disability, behind back pain and headache disorder (1). The economic burden was estimated at $326.2 billion in 2018 and continues to grow each year (2). However, there are a broad range of available interventions that have demonstrated efficacy and effectiveness. Unfortunately, a large proportion of people with depressive disorders do not receive adequate care. A survey of U.S. households found that only 29% of persons who screened positive for depression received treatment (3). This finding emphasizes the need to ensure that providers and patients have knowledge of and access to effective interventions and that treatment is appropriately made available to those with the greatest need. Of particular concern is evidence that there are extensive disparities in access to treatment for depressive disorders, with Hispanic Americans being three quarters as likely and African Americans being half as likely as White Americans to receive treatment (4).

The development and implementation of clinical practice guidelines (CPGs) have been identified as best practices for health care (5). In 1998, Congress directed the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD) to begin a partnership to develop CPGs to support the care of people with chronic diseases. This article describes key updates to the guidelines for managing depression, which include recommendations for screening, monitoring, appropriate treatment setting, and treatment choices. The previous version of this guideline was the most frequently viewed CPG on the ECRI Guidelines Trust guideline repository website, with 1695 hits during January through December of 2021 (Mathews K. Personal communication.).

Guideline Development Process

The development of all VA/DoD guidelines is directed by the Evidence-Based Practice Guideline Work Group and adheres to the standards for trustworthy guidelines that were set by the National Academy of Medicine (6). Senior leaders within the VA and DoD selected a multidisciplinary work group of practicing clinician stakeholders and clinical researchers from within the 2 departments to update this guideline. The work group included internal medicine, neuropsychiatry, nursing, pharmacy, psychiatry, psychology, sleep medicine, and social work. The work group was asked to disclose any conflicts of interest before the first group meeting and again at each subsequent meeting. The members of the work group did not identify any financial conflicts of interest. Several work group members had intellectual conflicts related to their research interests; these conflicts were mitigated by recusal from evidence discussions related to those areas. In addition, a patient focus group was convened to assess important aspects of treatment for patients and to gain information about patient values and preferences. The Lewin Group, a contracted third party with expertise in CPG development, facilitated meetings and the development of key questions using the PICOTS (population, intervention, comparison, outcome, timing, and setting) format. A consensus process was used to develop 12 key questions, which guided the evidence review and the subsequent recommendation development. Consensus was achieved among the work group through an iterative process involving discussions on conference calls. An independent third party, ECRI,

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conducted the systematic evidence review, which the guideline work group then used to develop recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (7–9). The GRADE approach incorporates 4 components to evaluate evidence and develop recommendations: confidence in the quality of the evidence; balance of desirable and undesirable consequences; patient values and preferences; and other considerations, such as feasibility, equity, and subgroup-specific needs. This approach requires that the recommendations are based on evidence and does not rely on unsystematic clinical observations. The search methods and results are detailed in the full guideline (www.healthquality.va.gov) (10).

Highlighted Changes in the Updated 2022 Guideline

A major change between the 2016 guideline and the updated 2022 guideline is how the management section is divided (10, 11). Previously, this section was divided into "treatment of uncomplicated mild to moderate MDD" and "treatment of severe, chronic, or recurrent MDD (complex)." The 2022 guideline refers to "treatment of uncomplicated MDD" and "treatment of MDD that is severe or has a partial or limited response to initial treatment." This updated organization of the recommendations aligns better with the body of evidence and clinical practice. In addition, several interventions that did not meet inclusion criteria or had a limited recommendation in the 2016 guideline now are included or have a higher-level recommendation. These include short-term psychodynamic psychotherapy (STPP) (Recommendation 7), trazodone (Recommendation 11), repetitive transcranial magnetic stimulation (rTMS) (Recommendation 17), second-generation antipsychotics (Recommendation 16), and ketamine or esketamine (Recommendation 19).

Treatment Decision Making

The CPG work group included 2 updated algorithms to assist with clinical decision making. **Figure 1** provides guidance for initial screening, evaluation, and treatment of uncomplicated depression or reinitiation of treatment for someone who previously was successfully treated. **Figure 2** provides guidance for treatment of patients who either are not initially responsive to care or have complicating factors that indicate a higher level of care. The redesign is intended to simplify decision making and align the algorithm flow with the updated recommendations.

Telehealth/Virtual Care

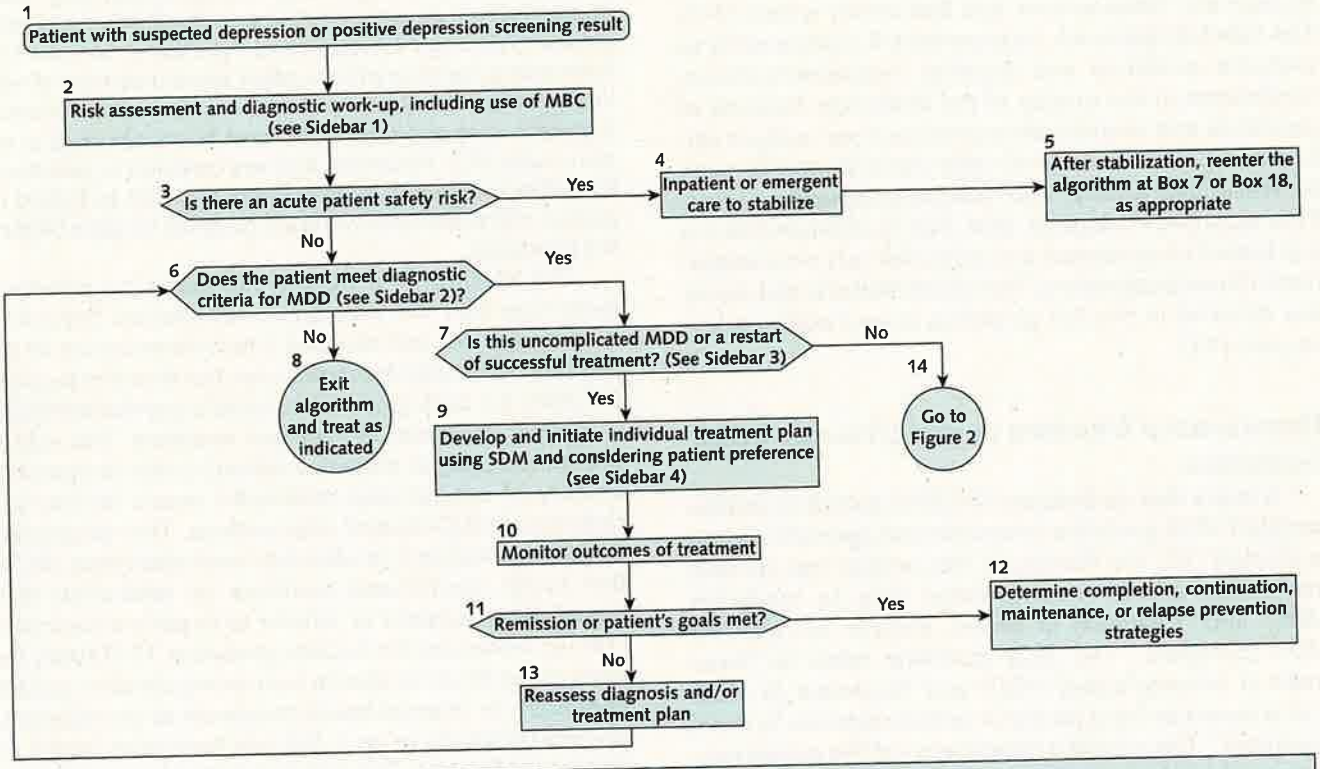
One of the most significant changes to health care delivery resulting from the COVID-19 pandemic is the increased reliance on telemedicine. Before the pandemic, there was modest use of clinician-delivered behavioral health telemedicine interventions for MDD, likely due to insurance and coding requirements (12). At the time of this publication, much of behavioral health care delivery includes some form of teleconferencing. Whether these changes and the accompanying reimbursement will persist once the pandemic has resolved is unclear. Although 43 states and the District of Columbia have laws governing private payer reimbursement of telehealth, those laws vary in requirements such as whether in-person care and telehealth must be reimbursed at the same rates (13). Assuming insurers continue to reimburse for behavioral health telemedicine, this shift to hybrid in-person and virtual care will likely continue to grow beyond the pandemic.

The VA/DoD CPG work group made it a priority to determine how this paradigm shift affected behavioral health outcomes and devoted 2 recommendations to the provision of virtually facilitated care. For Recommendation 5 (**Table**), the work group was unable to say that telehealth is superior or inferior to in-person treatment. This reflects the limited body of evidence related to the comparative efficacy of synchronous telehealth versus face-to-face delivery of MDD-related interventions. This recommendation is based on 3 randomized controlled trials (RCTs) that found inconclusive evidence on telehealth visits being either superior or inferior to in-person treatment (14–16). However, for Recommendation 10 (**Table**), the work group found evidence supporting clinician-guided computer- or internet-based treatment as an adjunct to pharmacotherapy or as a first-line treatment based on patient preference. This was supported by a systematic review that examined data on guided and unguided internet-based cognitive behavioral therapy (CBT) and concluded that it is an effective first-line approach (17). These recommendations highlight the larger body of evidence related to the asynchronous delivery of MDD interventions (such as CBT-related smartphone applications) compared with synchronous delivery methods.

Many of the studies contributing to this guideline update were completed before the pandemic. The only synchronous studies that met our inclusion criteria addressed behavioral activation. Behavioral activation focuses on asking patients to physically engage with and move about their environment; therefore, beginning with a telemedicine platform might help them overcome the lack of motivation associated with MDD. In time, a clinician may wish to transition to a face-to-face paradigm. This has not been studied, and we were unable to provide a clear recommendation. Although there are no clear outcomes favoring synchronous telemedicine over face-to-face care, no harms associated with telemedicine were identified in the studies that were reviewed. For patients who are underserved or homebound, telemedicine may be the best way to provide services to them.

Many factors influence the relative effectiveness of synchronous telemedicine, including patient comfort and familiarity with health care technologies. As a result, even though the work group found great potential for synchronous telemedicine, the evidence base was insufficient to make a recommendation. The work group expects that ongoing trials will provide more information on this in the future.

Figure 1. Initial assessment and treatment.



Sidebar 1: Risk Assessment and Work-up
Functional status, medical history, treatment history, and relevant family history Consider administration of PHQ-9 Evaluate for suicidal and homicidal ideation and history of suicide attempts, and consult the VA/DoD clinical practice guideline on assessment and management of patients at risk for suicide as appropriate Rule out depression secondary to other causes (e.g., hypothyroidism, vitamin B_{12} deficiency, syphilis, pain, chronic disease) Incorporate MBC principles in the initial assessment
Sidebar 2: DSM-5 Criteria
Criterion A: ≥5 of the following symptoms present during the same 2-week period; ≥1 of the symptoms is either depressed mood or loss of interest/pleasure: Depressed mood most of the day, nearly every day Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day Significant weight loss when not dieting, or weight gain Insomnia or hypersomnia nearly every day Psychomotor agitation or retardation nearly every day Fatigue or loss of energy every day Feelings of worthlessness or excessive inappropriate guilt Diminished ability to think, diminished ability to concentrate, or indecisiveness nearly every day Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a suicide attempt, or a specific plan for committing suicide Criterion B: The symptoms cause significant distress or functional impairment Criterion C: The episode is not attributable to the physiologic effects of a substance or another medical condition
Sidebar 3: Factors to Be Considered in Treatment Choice
Prior treatment response Severity (e.g., PHQ-9) Chronicity Comorbidity (e.g., substance use, medical conditions, other psychiatric conditions) Suicide risk Psychosis Catatonic or melancholic features Functional status Tolerability of prior treatments
Sidebar 4: Considerations in Treatment of Uncomplicated MDD
Consider collaborative/integrated care in primary care for appropriate patients For initial treatment, select pharmacotherapy or psychotherapy based on SDM If previous treatment was successful, consider restarting this approach Based on patient preferences, consider self-help with exercise (e.g., yoga, tai chi, qi gong, resistance, aerobics), patient education, light therapy, or bibliotherapy as an adjunct to psychotherapy or pharmacotherapy or as an alternative if first-line treatments are not acceptable and/or available Include patient characteristics (e.g., treatment of co-occurring conditions, cultural factors, social determinants, patients who are pregnant, geriatric patients) in SDM

DoD = U.S. Department of Defense; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MBC = measurement-based care; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9; SDM = shared decision making; VA = U.S. Department of Veterans Affairs.

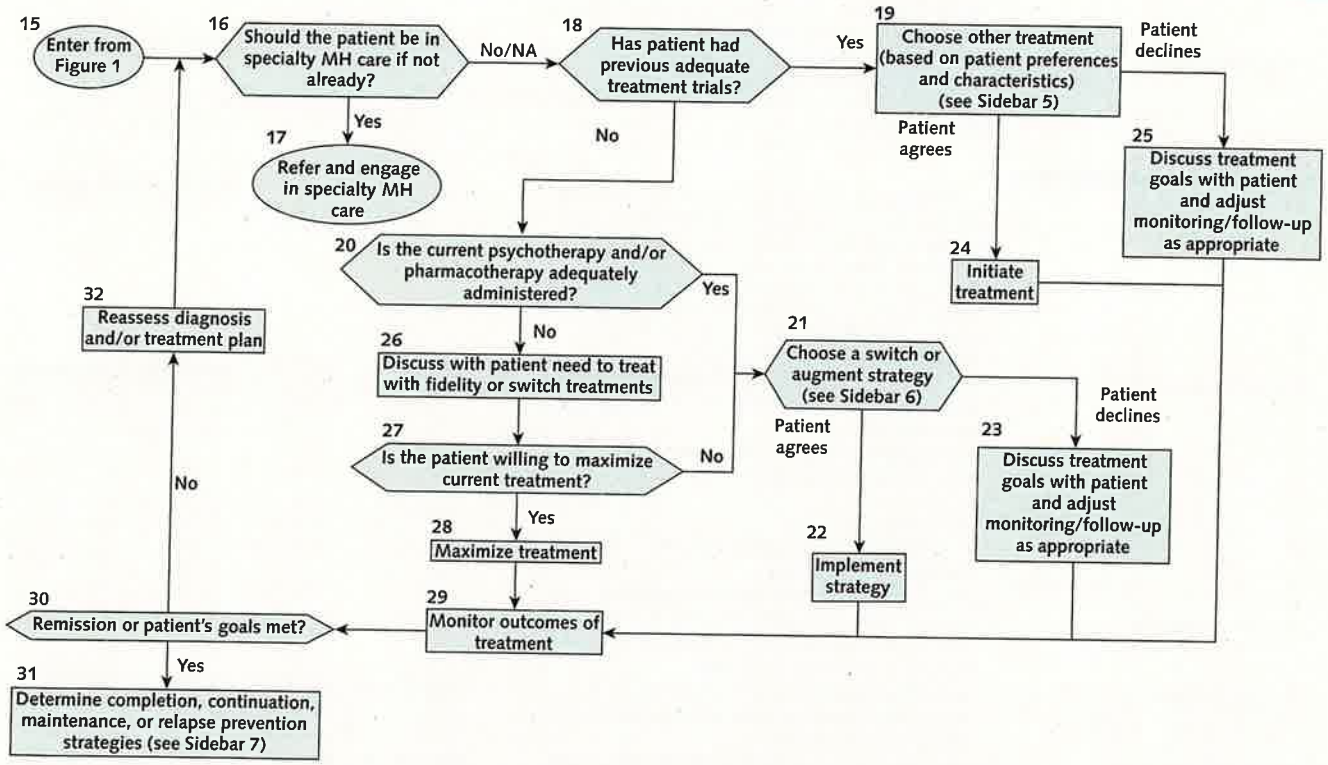
Psychotherapy

In the prior guideline, 6 forms of psychotherapy were recommended for initial treatment of depression, including (in alphabetical order) acceptance and commitment therapy, behavioral therapy/behavioral activation, CBT, interpersonal psychotherapy, mindfulness-based cognitive therapy, and problem-solving therapy. The evidence review supported continuing to recommend these therapies. In addition, the updated guideline includes a recommendation for STPP as an initial treatment option for uncomplicated MDD (Recommendation 7; **Table**). This update was based on 2 new randomized controlled noninferiority trials comparing STPP and CBT (18, 19). Of the selected psychotherapies, the evidence did not suggest that any of them are more effective than any other in reducing depressive symptoms or achieving remission. There were also no specific CBT packages that offered notable advantages over traditional CBT, such as metacognitive therapy or cognitive evolutionary therapy (20, 21). Group and individual delivery methods seemed to provide similar outcomes. Factors such as patient preferences, past experience with treatment, and provider training should be considered when selecting specific approaches.

Bright Light Therapy

The updated guideline recommends bright light therapy for persons with mild to moderate MDD, regardless

Figure 2. Advanced care management.



Sidebar 5: Treatment Options for Patients Who Have Not Responded to Adequate Treatment Trials*
Consider the following treatment options: Other pharmacotherapy options (e.g., MAOIs, TCAs) (see Recommendation 16) ECT (see Recommendation 20) rTMS (see Recommendation 17) Ketamine/esketamine (see Recommendation 19)
Sidebar 6: Treatment Options for Switching or Augmenting
Consider the following treatment options: Adding psychotherapy or an antidepressant Switching to a different treatment (e.g., switch between psychotherapy or pharmacotherapy, switch to a different focus of psychotherapy or different antidepressant) Augmenting with a different class of medication (e.g., adding an SGA)
Sidebar 7: Treatment Options During Remission
Consider the following treatment options: For patients treated with antidepressants, consider continuation at the therapeutic dose for ≥6 mo For patients with high risk for relapse, regardless of prior treatment received, consider offering a course of CBT

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; MH = mental health; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; SGA = second-generation antipsychotic; TCA = tricyclic antidepressant.
* Patients who have shown partial or no response to initial pharmacologic monotherapy (maximized) after a minimum of 4 to 6 weeks.

Table. VA/DoD Clinical Practice Guideline on Management of Major Depressive Disorder

Topic	Recommendation	Strength	Category
Screening			
Recommendation 1	We suggest that all patients not currently receiving treatment for depression be screened for depression.	Weak for	Not reviewed, amended
Monitoring outcomes			
Recommendation 2	For patients with MDD, we suggest using a quantitative measure of depression severity in the initial treatment planning and monitoring treatment progress at regular intervals to guide shared treatment decision making.	Weak for	Reviewed, new/replaced
Treatment setting			
Recommendation 3	For patients with MDD who are being treated in the primary care setting, we recommend the use of collaborative/integrated care models.	Strong for	Reviewed, amended
Recommendation 4	For patients with MDD, there is insufficient evidence to recommend for or against the use of a team-based model in specialty mental health care settings.	Neither for nor against	Reviewed, new/added
Recommendation 5*	For patients with MDD, there is insufficient evidence to conclude that interventions delivered by clinicians using telehealth are either superior or inferior to in-person treatment.	Neither for nor against	Reviewed, new/added
Treatment of uncomplicated MDD			
Recommendation 6	We recommend that MDD be treated with either psychotherapy or pharmacotherapy as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies, such as augmentation, combination treatment, switching of treatments, or use of non-first-line treatments (see Recommendations 17, 18, and 20).	Strong for	Reviewed, new/replaced
Recommendation 7*	When choosing psychotherapy to treat MDD, we suggest offering one of the following interventions (not rank ordered): • Acceptance and commitment therapy • Behavioral therapy/behavioral activation • CBT • Interpersonal therapy • Mindfulness-based cognitive therapy • Problem-solving therapy • Short-term psychodynamic psychotherapy	Weak for	Reviewed, new/replaced
Recommendation 8	For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.	Weak for	Reviewed, not changed
Recommendation 9	There is insufficient evidence to recommend for or against combining components from different psychotherapy approaches.	Neither for nor against	Reviewed, new/added
Recommendation 10*	For patients with mild to moderate MDD, we suggest offering clinician-guided computer- or internet-based CBT either as an adjunct to pharmacotherapy or as a first-line treatment, based on patient preference.	Weak for	Reviewed, new/replaced
Recommendation 11	When choosing an initial pharmacotherapy, or for patients who have previously responded well to pharmacotherapy, we suggest offering one of the following (not rank ordered): • Bupropion • Mirtazapine • A serotonin–norepinephrine reuptake inhibitor • Trazodone, vilazodone, or vortioxetine • A selective serotonin reuptake inhibitor	Weak for	Reviewed, new/replaced
Recommendation 12	When choosing an initial pharmacotherapy, we suggest against using: • Esketamine • Ketamine • MAOIs • Nefazodone • TCAs	Weak against	Reviewed, new/added

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Topic	Recommendation	Strength	Category
Recommendation 13*	There is insufficient evidence to recommend for or against pharmacogenetic testing to help guide the selection of antidepressants.	Neither for nor against	Reviewed, new/added
Recommendation 14	For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies (either in-person or virtually), we suggest nondirective supportive therapy.	Weak for	Not reviewed, amended
Treatment of MDD that is severe or has a partial or limited response to initial treatment			
Recommendation 15	We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD characterized as: • Severe (e.g., PHQ-9 score >20) • Persistent (duration >2 y) • Recurrent (≥2 episodes)	Weak for	Not reviewed, amended
Recommendation 16	For patients with MDD who have shown partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered): • Switching to another antidepressant (including TCAs, MAOIs, or those in Recommendation 12) • Switching to psychotherapy • Augmenting with a psychotherapy • Augmenting with a second-generation antipsychotic	Weak for	Reviewed, amended
Recommendation 17*	For patients who have shown partial or no response to ≥2 adequate pharmacologic treatment trials, we suggest offering repetitive transcranial magnetic stimulation for treatment.	Weak for	Reviewed, amended
Recommendation 18*	There is insufficient evidence to recommend for or against theta-burst stimulation for the treatment of MDD.	Neither for nor against	Reviewed, new/added
Recommendation 19*	For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine for augmentation.	Weak for	Reviewed, new/replaced
Recommendation 20	We recommend offering ECT with or without psychotherapy for patients with severe MDD and any of the following conditions: • Catatonia • Psychotic depression • Severe suicidality • A history of a good response to ECT • Need for rapid, definitive treatment response on either medical or psychiatric grounds • The risks associated with other treatments are greater than the risks of ECT for the specific patient (i.e., co-occurring medical conditions make ECT the safest MDD treatment alternative) • A history of a poor response or intolerable adverse effects to multiple antidepressants	Strong for	Reviewed, not changed
Relapse prevention/continuation phase (all severities and complexities)			
Recommendation 21	For patients with MDD who achieve remission with antidepressants, we recommend continuation of antidepressants at the therapeutic dose for ≥6 mo to decrease risk for relapse.	Strong for	Not reviewed, not changed
Recommendation 22	For patients with MDD at high risk for relapse or recurrence (e.g., ≥2 prior episodes, unstable remission status), we suggest offering a course of CBT, interpersonal therapy, or mindfulness-based cognitive therapy during the continuation phase of treatment (i.e., after remission is achieved). The evidence does not support recommending 1 of these 3 evidence-based psychotherapies over another.	Weak for	Not reviewed, amended

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Topic	Recommendation	Strength	Category
Recommendations for specific populations			
Recommendation 23	For patients with mild to moderate MDD who are breastfeeding or pregnant, we recommend offering an evidence-based psychotherapy as a first-line treatment (see Recommendation 7). In patients with a history of MDD before pregnancy who responded to antidepressant medications and are currently stable on pharmacotherapy, weigh risk-benefit balance to both mother and fetus in treatment decisions.	Strong for	Not reviewed, amended
Recommendation 24	For older adults (≥65 y) with mild to moderate MDD, we suggest offering a first-line psychotherapy (see Recommendation 7). Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision.	Weak for	Not reviewed, amended
Recommendation 25	For patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy.	Weak for	Not reviewed, amended
Recommendation 26*	For patients with mild to moderate MDD with or without a seasonal pattern (formerly seasonal affective disorder), we suggest offering bright light therapy.	Weak for	Reviewed, new/replaced
Self-help, complementary, and alternative treatments			
Recommendation 27	For patients with MDD, we suggest exercise (e.g., yoga, tai chi, qi gong, resistance, aerobics) as an adjunct.	Weak for	Reviewed, new/replaced
Recommendation 28	For patients with MDD, we suggest CBT-based bibliotherapy as an adjunct to pharmacotherapy or psychotherapy or as an alternative when patients are unwilling or unable to engage in other treatments.	Weak for	Reviewed, amended
Recommendation 29	For patients with mild MDD who are not pregnant or breastfeeding and who prefer herbal treatments to first-line psychotherapy or pharmacotherapy, we suggest standardized extract of St. John's wort as monotherapy.	Weak for	Not reviewed, amended
Recommendation 30	For patients with MDD, there is insufficient evidence to recommend for or against acupuncture as an adjunct.	Neither for nor against	Reviewed, new/replaced
Recommendation 31	For patients with MDD, there is insufficient evidence to recommend for or against the addition of biofeedback.	Neither for nor against	Reviewed, new/added
Recommendation 32	For patients with MDD, there is insufficient evidence for or against the use of meditation as an adjunct.	Neither for nor against	Reviewed, new/added
Other treatments with a recommendation against use			
Recommendation 33	For patients with MDD, we suggest against using vagus nerve stimulation outside a research setting.	Weak against	Reviewed, amended
Recommendation 34	For patients with MDD, we recommend against using deep-brain stimulation outside a research setting.	Strong against	Reviewed, not changed
Recommendation 35*	Given the limited information on the safety and efficacy of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments, we recommend against using these agents for MDD outside a research setting.	Strong against	Reviewed, new/added
Recommendation 36	We suggest against using omega-3 fatty acids or vitamin D for treatment of MDD.	Weak against	Not reviewed, not changed

CBT = cognitive behavioral therapy; DoD = U.S. Department of Defense; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9; TCA = tricyclic antidepressant; VA = U.S. Department of Veterans Affairs.
* Discussed in the guideline synopsis manuscript.

of seasonal pattern or seasonal component (Recommendation 26; Table). The previous guideline recommended bright light therapy only for those with a seasonal pattern. This updated recommendation was based on evidence from a systematic review of 1200 patients as well as 2 RCTs cited in the previous guideline that showed similar results in patients without a seasonal element (22–24). Bright light therapy can be used in combination with other treatments or as monotherapy for treatment of MDD. There was low confidence in the evidence due to notable limitations, such as lack of blinding, unclear allocation concealment, and small sample size. However, the benefits of bright light therapy outweighed any potential harm, which led to the recommendation.

rTMS and Theta-Burst Stimulation

A review of the current literature on rTMS did not change the 2016 recommendation that suggested its use among patients with MDD who have shown partial or no response to 2 or more adequate pharmacologic treatment trials (Recommendation 17; **Table**); however, the work group found insufficient evidence to make a recommendation for or against use of theta-burst stimulation (TBS) (Recommendation 18; **Table**). A review of the evidence that was included in the previous guideline showed a significantly higher response and remission rate for rTMS compared with sham treatment, with a number needed to treat of 3.4 to 9 patients for response and 5 to 7 patients for remission (25–27). Of note, 1 more recent RCT that was specific to a veteran population found no significant differences between rTMS and sham treatment (28). The study compared up to 30 treatment sessions of left prefrontal rTMS versus sham control treatments in 164 patients with treatment-resistant depression (TRD), with high rates of comorbid posttraumatic stress disorder and substance use disorder among the study population. The study found significant reductions in depressive symptoms and high remission rates after treatment (39% overall). However, no significant differences in these outcomes were seen between rTMS and sham therapies at treatment completion or at 24 weeks, as measured in intention-to-treat analyses using the clinician-administered or self-report depression symptom measures. There were also no significant differences when data were stratified by presence of posttraumatic stress disorder. This study raises the possibility that placebo effects, possibly due to factors such as expectancy and the clinical attention from the frequency of visits required for this treatment, play an important role in rTMS outcomes. However, the work group did not believe that this single study was sufficient to modify the prior recommendation. The aggregate literature suggested that the benefits of rTMS for TRD in improving symptoms and facilitating remission outweigh the harms, with only minimal and manageable adverse events. The work group also noted that one of the primary challenges for rTMS is access to this treatment given that it requires frequent onsite visits.

Theta-burst stimulation is a variation of TMS that uses rapid, repetitive pulses. An RCT by Chou and colleagues investigating the antidepressant efficacy of bilateral TBS monotherapy found that TBS showed statistically significant improvement over sham stimulation after 12 weeks but no differences at 24 weeks in the critical outcome of remission of depressive symptoms (29). However, the strength of the evidence for the outcomes assessed was very low due to the small sample size and the indirect measurement of the critical outcome. A study of the clinical effectiveness, safety, and tolerability of intermittent TBS (iTBS) compared with standard 10-Hz rTMS in adults with TRD showed that 10-Hz rTMS did not provide more benefit than iTBS (30). However, given the limited sample size, the work group was unable to recommend for or against the use of iTBS (Recommendation 18; **Table**).

Ketamine and Esketamine

One significant change in the 2022 CPG is a new recommendation to suggest ketamine or esketamine as a treatment option in patients who have not responded to several adequate pharmacologic trials (Recommendation 19; **Table**). The 2016 guideline recommended against the use of ketamine to treat MDD outside research settings while noting there was a gap in knowledge related to its use. Esketamine was not commercially available when the previous guideline was written; therefore, it was not included.

Current evidence suggests that both ketamine infusion and intranasal esketamine improve depressive symptoms in patients with MDD for whom at least 2 previous adequate trials of antidepressant medications have failed (31–33). A meta-analysis of 20 RCTs evaluated the efficacy of single-dose ketamine in different subgroups to establish whether repeated administration of ketamine could be a viable strategy to maintain treatment gains (32). The authors found that, compared with placebo or midazolam (4 studies), ketamine used as monotherapy or in conjunction with an antidepressant in patients with TRD resulted in significant improvement in depressive symptoms after 24 hours. These improvements persisted at 3- and 4-day follow-up visits. Significant improvements compared with controls were observed for up to 7 days in the TRD group when ketamine was added to ongoing antidepressant treatment; however, there were no significant differences at 7 days when ketamine was used as monotherapy. These results complement the VA/DoD CPG for the assessment and management of patients at risk for suicide, which supports ketamine infusions as an adjunctive treatment for short-term reduction in suicidal ideation in patients with suicidal ideation and MDD (34).

A meta-analysis of 5 RCTs examining esketamine as augmentation therapy found that twice-weekly dosing of esketamine as augmentation to ongoing oral antidepressant use improved depressive symptoms and remission rates in patients with MDD at up to 28 days of follow-up (31). These results were only seen in patients with TRD and those with new or optimized antidepressant therapy. Esketamine is also approved for the treatment of depressive symptoms in adults with MDD and acute suicidal ideation or behavior. However, the effectiveness of esketamine in preventing suicide or reducing suicidal ideation or behavior has not been established (35, 36).

Ketamine lacks long-term efficacy and safety trials in MDD, and the bulk of the evidence on short-term (7-day) efficacy is from studies in patients who have previously not responded to adequate trials of antidepressants. Although there is evidence to support longer-term maintenance use of esketamine, it too has been primarily studied in patients who have previously not responded to trials of antidepressants (37, 38). Unlike ketamine, esketamine has risk evaluation and mitigation strategy requirements, which include requirements for pharmacy, health care setting certification, and mandatory monitoring for 2 hours after treatment. Ketamine and esketamine are not recommended as initial treatment but are reserved for patients for whom previous therapies have failed or who have not tolerated previous therapies (32).

This recommendation reflects the balance of consistent evidence of benefit weighed against the risks for adverse effects and the limited information on the long-term consequences of ketamine or esketamine therapy. Additional information about long-term outcomes will be particularly beneficial for future evaluations of these medications.

Interventions Considered but Not Recommended at This Time

Psilocybin/Hallucinogens

The literature search for research on hallucinogens for the treatment of depression produced 1 study of psilocybin with 27 participants. The study compared participants randomly assigned to immediate therapy with psilocybin versus those who received psilocybin after an 8-week waiting period. Supportive psychotherapy was also provided throughout the psilocybin treatment. Those who completed the study in the immediate psilocybin group (n = 13) had significantly improved depressive symptoms at weeks 5 and 8 (39).

Therapeutic use of psilocybin requires health care providers to help prepare and then guide the patient through the treatment. Treatment interventions usually last 8 to 12 hours. Some concerns with psilocybin therapy are the risk for psychotic events and harmful behaviors in patients who do not receive appropriate guidance throughout the treatment process (39) and the potential for dependence. Given the limited evidence related to psilocybin safety and efficacy, the guideline recommends against its use. The work group also recommends against the use of MDMA, cannabis, or other unapproved pharmacologic agents in settings outside clinical trials (Recommendation 35; **Table**). Trials in veterans are currently under way and may provide more clarity on the utility of psilocybin in the future.

Pharmacogenomic Testing

The work group reviewed evidence on the use of pharmacogenomic testing as a guide for selecting antidepressants. The work group determined there was not sufficient evidence to make a recommendation either for or against its use (Recommendation 13; **Table**). Although there is extensive interest in developing approaches to better match patients to treatments, only 1 systematic review that included 4 RCTs and 2 open-label trials was available, along with limited additional RCTs. Overall, the findings were mixed in terms of outcomes, and the quality of evidence was very low due to small sample sizes and concerns about potential bias because the studies were commercially funded. In particular, the work group noted that studies of pharmacogenomic testing need to oversample populations because test results are relevant for only about 15% to 20% of participants being considered for medication. As a result, the current studies in our review had too few events to confirm or rule out an effect. Although there was evidence suggesting some benefit to pharmacogenetic matching (40, 41), the work group determined that it was not enough to make a recommendation.

Gaps in the Literature

Researched Populations

Despite increased recognition of the need for studies to be inclusive in terms of factors such as gender, sexual orientation, race, ethnicity, age, disability status, socioeconomic factors, and rurality, we did not find enough evidence to make recommendations for these subgroups. This can lead to interventions that maintain or exacerbate poor outcomes or disparities in health care. For example, although we did not find clear evidence comparing telehealth and in-person care, during the pandemic, telehealth has been important in providing access to care that otherwise would not have been delivered. Future studies that include a broad range of patients in ongoing evaluations of telehealth will be critical to determine how to prioritize treatment options for different patient populations.

Treatment Comparisons

The guideline work group found several key comparisons for which there was limited research. Leveraging technology as a therapeutic intervention in various forms to include guided self-help, synchronous telehealth, and computerized interventions and comparisons of these interventions are high priorities given the proliferation of these different approaches.

There is also a need for more study of psychotherapy that includes examination of treatment formats (for example, group vs. individual). At a conceptual level, the work group recognizes the limitations of studies that are structured around specific manualized interventions. Future research should evaluate what components of psychotherapy contribute to successful treatment response and whether formulation or conceptualization can improve outcomes.

The work group also noted a broad range of areas for research in pharmacotherapy. These included well-designed rigorous trials of unapproved pharmacologic agents, either alone or in combination with psychotherapy. Studies that examined alternative and complementary interventions were also limited. Despite extensive interest in these modalities, many of the studies were poorly designed and of little value.

Comparison of Major Depression Guidelines

The VA/DoD CPG on MDD has significant overlap with other major guidelines as well as important differences. Three relevant comparators are depression guidelines from the American Psychological Association (APA) (42), the American College of Physicians (ACP) (43), and the U.K. National Institute for Health and Care Excellence (NICE) (44). The APA guideline provides separate recommendations for adolescents, adults, and older adults. It also addresses the efficacy of psychotherapy and complementary and alternative medicine interventions and includes a comparative effectiveness analysis of those interventions versus pharmacotherapy. The ACP guideline examines the comparative effectiveness of nonpharmacologic (psychotherapy and complementary and

alternative medicine) and pharmacologic treatments for adults either alone or in combination. The recently updated NICE CPG includes recommendations for adults covering 9 domains: service delivery, treatment of a new episode of depression, preventing relapse, further-line treatment, chronic depression, depression comorbid with personality disorder, psychotic depression, access to services, and patient choice. The VA/DoD and NICE CPGs have a broader focus addressing interventions, care setting, and method of care. The APA and ACP guidelines focus primarily on the comparative effectiveness of pharmacologic and nonpharmacologic interventions.

Although these CPGs agree on some basic principles, there are also meaningful differences. The VA/DoD, APA, and NICE guidelines all recommend a range of psychotherapies for treatment of depression; however, the ACP guideline only recommends CBT, citing insufficient evidence to support other therapies. The VA/DoD guideline is also the only one among the four that addresses the use of ketamine, esketamine, and psychedelics in the treatment of depression. The guideline suggests use of ketamine and esketamine in patients who have not responded to other treatments and recommends psychedelic treatments only in a research setting. Interventional treatments are addressed only by the VA/DoD and NICE CPGs. Both guidelines recommend electroconvulsive therapy in similar contexts (for example, multiple prior treatment failures or need for rapid improvement).

Many of the differences among the guidelines are related to the age of their evidence reviews. The ACP and APA guidelines were based on literature reviews ending in 2015, and there has been extensive additional research in relevant domains since then. The VA/DoD guideline, which has the most recent evidence review, extends beyond other guidelines, with the update on initial treatment options; the examination of modalities of care, such as telemental health; and the focus on interventional treatments and use of psychedelic interventions.

CONCLUSION

We hope the updated CPG will improve treatment decision making and inform future research directions. The guideline work group found a broad and expanding range of treatment options for major depression. The expansion of psychotherapy options, the inclusion of ketamine and esketamine as interventions for patients who have not responded to pharmacologic options, and the expansion of the recommendation for bright light therapy increase choices for patients and providers. In addition, considerations regarding psychedelic medications, pharmacogenomics, treatment modalities, and the lack of sufficient information to address specific patient populations highlight areas requiring additional research.

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Annals of Internal Medicine

How Would You Screen This Patient for Colorectal Cancer?

Grand Rounds Discussion From Beth Israel Deaconess Medical Center

Risa B. Burns, MD, MPH; Carol M. Mangione, MD, MSPH; David S. Weinberg, MD, MSc; and Zahir Kanjee, MD, MPH

Colorectal cancer (CRC) is the third leading cause of cancer death for men and women in the United States, with an estimated 52 580 people expected to die in 2022. Most frequently, CRC is diagnosed among persons aged 65 to 74 years. However, among persons younger than 50 years, incidence rates have been increasing since the mid-1990s. In 2021, partially because of the rising incidence, the U.S. Preventive Services Task Force (USPSTF) recommended CRC screening for adults aged 45 to 49 years (Grade B recommendation). Options for CRC screening include stool-based and direct visualization tests. The USPSTF did not recommend a specific screening test; rather, its guidance was to select a test after a discussion with the patient. Here, a primary care physician and a gastroenterologist discuss the recommendation to begin CRC screening at age 45, review options for CRC screening, and discuss how to choose among the available options.

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ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is a multimedia feature based on selected clinical conferences at Beth Israel Deaconess Medical Center (BIDMC). Each educational feature focuses on the care of a patient who "falls between the cracks" in available evidence and for whom the optimal clinical management is unclear. Such situations include those in which a guideline finds evidence insufficient to make a recommendation, a patient does not fit criteria mapped out in recommendations, or different organizations provide conflicting recommendations. Clinical experts provide opinions and comment on how they would approach the patient's care. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit Annals.org/GrandRounds.

This article is based on the Medical Grand Rounds conference held on 14 April 2022.

Ms. N is a 44-year-old woman with a history of hypertension, migraine headaches, and gastroesophageal reflux. At a recent annual examination, her primary care physician (PCP) recommended colorectal cancer (CRC) screening. Ms. N is married and has 2 children at home. She has no family history of CRC or colonic polyps. She has undergone routine screening for breast and cervical cancer. She works full-time and is trying to walk for exercise. She reports no tobacco or alcohol use. Ms. N is unsure how to decide among available options for CRC screening.

Ms. N's Story (Video at Annals.org)

See the Patient Video (Video 1, available at Annals.org) to view the patient telling her story.

At my most recent visit, my PCP brought up that the age for colon cancer screening had been lowered from 50 to 45 and I was just about to turn 45. She asked me if I would like to get screened and I didn't know really much about anything. I had a few friends who are older than me who had gotten screened, so I knew that there was a pretty heavy preparation process for it, but I wasn't aware that I had options. My PCP explained that I could have a colonoscopy or that I could use a stool DNA test. I don't think it's as effective a screening process, but it is another option that would not be as invasive, I believe. At that appointment, I told her that I would be comfortable getting a colonoscopy because it was all I knew about. I

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